Biomarkers for the response to immunotherapy in patients with non-small cell lung cancer

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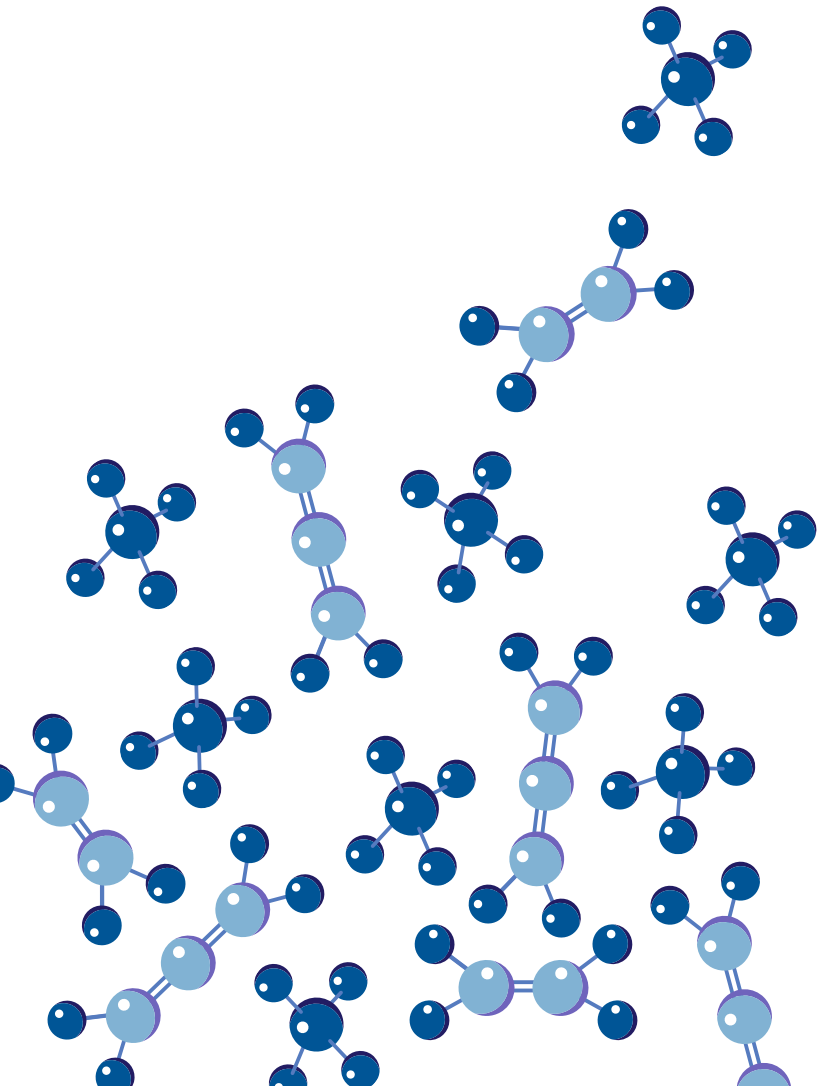

7 I love my dog, editorial

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In many households, a dog is part of the family. The dog protects you, makes sure you will get your exercise while taking him for a walk and if lucky, and gets the paper for you on a Saturday morning. Nowadays dogs are more than just a pet, mostly because of their well-known good scent. By entering the US or Australia, dogs are used to identify drug-carriers or persons trying to import food.

People use a dog's outstanding sense of smell in many ways. The olfactory capability of dogs is about 10.000-100.000 times better than human beings. Whereas the human only has 5 million scent receptors, the nose of a bloodhound contains about 300 million olfactory receptors[268]. Even with a low limit of detectability for volatile organic compounds (VOCs) of one part per trillion (1×10^{12}), dogs are able to smell multiple different odors [269, 270]. Dogs are already being used in daily clinical practice. In the United States, Dogs4Diabetics train dogs for early recognition of hypoglycemia, so that a patient can take action in time. Some dogs are trained to recognize the start of an epileptic insult, to help a patient finding a better and safer environment.

In the last decades, research is committed to basically copy the nose of a dog by developing electronic devices, so called electronic noses (e-nose), for the detection and recognition of odors and flavors. Exhaled breath of humans contains thousands of VOCs that originate from metabolic processes[227] , which can be detected with such devices. Multiple studies show that with the analysis of exhaled breath it is possible to differentiate between patients with different diseases like COPD, asthma, lung cancer compared to healthy subjects [65, 271-273]. Still, it has its limitations. One of the theories how the human scent works, is that we are not able to detect individual VOCs per se, but recognize a pattern. One example is that we recognize an orange as an orange and can differentiate it from a clementine, although we do not know which VOCs cause that specifically. However, in general the difficulty is that with all the current methods, we are not able to find and validate a pattern in multiple studies. To analyze VOCs by molecule GC-Mass Spectroscopy is required. This is complicated, expensive, time consuming and needs data analysis. Also, in multiple studies, multiple different important VOCs are found [274]. An alternative is to analyze multiple gasses simultaneously by using special sensors. This approach has gained popularity, but due to lack of standardization, studies cannot easily be compared.

In a previous paper, Guirao et al [275] presented the use of a dog trained identify patients with lung cancer. He was able to identify patients with lung cancer smelling their exhaled breath. Besides lung cancer, there were two control groups: patients with lung diseases like COPD and healthy subject. The results were impressive with a sensitivity of 95% and a specificity of 98%. Using exhaled breath analysis would be of great importance in diagnosing (early) disease and response monitoring. Until now there are no general accepted screening methods available in Europe. In the US screening programs are available, but the number needed to screen with CT scan is still 1:320 [276]. In the Netherlands, the NELSON-trial investigates the benefits of screening with a CT-scan compared to a control group. They found a survival benefit in the screened group, which was 26% better after 10 years for the male participants [277]. For females, the survival benefit was even better (41.8%), although not significant [278]. However, with a CT-scan, nodules are found where the distinction between benign and malignant is very difficult. The key question is if a dog can discriminate if a solitary pulmonary nodule is benign or malignant. Therefore, in their follow-up study published in the current issue

of Lung Cancer, they used the same dog for the discrimination between malignant and benign lesions [279]. Thirty patients participated in this study. Again, they reached a very high sensitivity and specificity, suggesting that the smell of lung cancer is quite specific.

Despite the benefits of the use of a dog, the question remains if this is a realistic option for clinical practice. For a start, you will need a dog from a breed which is known for its good scent. You will need to train and nurture it, which is a time consuming activity. And how do we deal with all the quality assurance? Is there a CE label for these dogs and how do we keep the quality high? Dogs are living beings and are subject to infections or other diseases. Will the analytic quality changes during the day or by aging and how many working hours is a dog allowed to function? These and many more practical factors urge us to seek other avenues of which the eNose is very popular. Processes of standardization and real time availability of the outcome will lead to a rise in the use of these machines.

In conclusion, with their outstanding good scent dogs are able to smell the small differences between multiple odors. Research is ongoing to contrive the added value in clinical practice for the recognition of lung cancer. And for your dog at home: Yes, your dog is able to smell the difference between, for example, whether or not you took a shower, and despite that, he will remain faithful to you and still like you. Therefore, the next unfortunate time he eats your paper on a Saturday morning, please keep this in mind and think “Yeah, I love my dog (too)”.